REMARKS/ARGUMENTS

1. Revised Claims.

Amended claims 1, 3, 16, 19, and 24 are submitted in which the subject matter of claims 2 and 5 to 8 have been cognated into claim 1. Claims 2 and 5 to 8 have consequently been cancelled. The limitation to radioactive imaging moieties can be found in the specification at page 4 lines 17 to 21. Claim 1 has also been amended to specify "An *in vivo* imaging agent …..". Basis can be found throughout the specification.

The preferred value of m (m=1) from page 1 line 1 of the specification has been inserted in Formula I, and 'm' removed to simplify the claim.

Claims 3, 19 and 24 have been amended to make them consistent with revised claim 1. Claim 16 has been amended to delete a phrase which is now redundant, given that revised claim 1 is limited to radioactive imaging moieties.

2. Claim Rejections: 35USC §112.

Claims 1, 2, 8-16, 18 and 26-29 stand rejected in this regard.

Applicants contend that the phrase "labeled with" in claim 1, when the label is a radiolabel, would be well known to the person skilled in the art of radiopharmaceuticals. Thus, the person would know that eg. when the radiolabel is ^{11}C, the ^{11}C carbon atom would be an intrinsic part of the chemical structure. When the radiolabel is a radiometal, "labeled

with" means attachment of a metal complex. When the radiolabel is eg. ^{18}F, it would be an ^{18}F atom bonded to an aryl or alkyl substituent etc.

Applicants also refer to claim 2, where the construction of the imaging agent is specified in Formula I.

Claim 11 is also consistent with the above, by stating that the "imaging moiety" is "attached to the R^2 substituent" [emphasis added].

In the light of the above, applicants contend that the subject matter of the claims is clear, and that the objection should therefore be withdrawn.

3. Claim Rejection: 35 USC §102.

3.1 Grunberg.

Claims 1, 2, 15, 16, 18 and 26-28 stand rejected as being anticipated by Grunberg et al. (US 3,952,091) (Grunberg).

Applicants refer to revised claim 1, which now specifies specific radioisotopes at (i), (ii) and (iii) therein. ^{125}I, as taught by Grunberg, is outside the scope. In addition, Grunberg is silent on *in vivo* imaging agents, which is an essential feature of revised claim 1. Revised claim 1 is therefore believed novel over Grunberg. The remaining claims all either depend on or refer to claim 1, and are therefore believed novel for the same reasons. The novelty objection based on Grunberg should therefore be withdrawn.

3.2 Adamczyk.

Claims 1, 2, 9, 11, 15 and 26-28 stand rejected as being anticipated by Adamczyk (US 6,472,227) (Adamczyk).

The Examiner has argued that Adamczyk discloses barbituric acid derivatives labeled at the 5-position with fluorescein. Adamcyzk was argued to anticipate previous claim 1 because the intended use was regarded as not patentably distinct.

Applicants refer to revised claim 1, where the "imaging moiety" is limited to specific radioisotopes at (i) – (iii). The subject matter is thus believed clearly novel over Adamczyk, since Adamczyk is silent on radioactive labels.

With respect to present claims 26-28, applicants point out that the kit of Adamczyk is described at Column 8 line 51 to Column 9 line 5 therein. Reference is made (column 8 lines 65-67) to the kit combining a "tracer". The formula of the tracer is stated to be Figure 27, with reference to the Summary of Invention. That text, at column 3 lines 4 to 25 requires that a fluorescein is attached. See the definitions at (3) and (4). Such a kit is outside the scope of present claim 26, since that kit requires a precursor suitable for reaction with a radioisotope.

The novelty objections based on Adamczyk should therefore be withdrawn.

3.3 Noe.

Claims 1, 2, 8, 15, 16, 18, and 26-28 stand rejected as being anticipated by Noe et al. (US 6,706,723) (Noe).

Applicants respectfully submit that claims 1, 16, and 24 have been amended to overcome any anticipation of Noe. Further, claims 2 and 8 have been cancelled to expedite prosecution. Applicants respectfully point out that Noe is silent on imaging, in particular *in vivo* imaging agents. Revised claim 1 is limited to such agents. Hence, the person skilled in the art in the field of radiopharmaceutical imaging agents could have no motivation to use Noe as suggested by the Examiner, since Noe is silent on imaging.

Noe teaches instead the use of ^{3}H or ^{14}C labels for "drug and/or substrate tissue distribution assays". (Column 20 lines 39-41 therein). Noe teaches that ^{3}H or ^{14}C are particularly preferred labels (Column 20 lines 41-43). Thus, Noe teaches away from the subject matter of the present claims.

The novelty objections based on Noe should therefore be withdrawn.

4. Claim Rejections: 35 USC §103.

4.1 Grams, Noe, Carpenter and Mobashery.

Claims 1, 2, 8-16, 18 and 26-28 stand rejected as being unpatentable over Grams [Biol. Chem., 382 p 1277-1285 (2001)] in view of Noe (US 6,706,723), in further view of Carpenter (US 6,656,448) and Mobashery (US 6,703,415).

Applicants first of all point out that Noe is silent on imaging, in particular *in vivo* imaging agents. Revised claim 1 is limited to such agents. Hence, the person skilled in the art in the field of radiopharmaceutical imaging agents could have no motivation to use Noe as suggested by the Examiner, since Noe is silent on imaging.

In fact, Noe teaches instead the use of ^{3}H or ^{14}C labels for "drug and/or substrate tissue distribution assays". (Column 20 lines 39-41 therein). Noe teaches that ^{3}H or ^{14}C are particularly preferred labels (Column 20 lines 41-43). Thus, Noe teaches away from the subject matter of the present claims.

The Examiner also suggests that Noe teaches isotopically labeled compounds, including specifically radiofluorinated at the 5-position of barbituric acid. Applicants disagree with that interpretation. Noe in fact teaches (column 20 lines 24 to 28) quite clearly that:

> "....one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}P, ^{18}F, and ^{36}Cl, respectively."

Thus, Noe itself clearly states that any position of the barbituric acid can be isotopically labeled. Since Noe includes isotopes of H, C, N, O, P, F and Cl, applicants

contend that the person skilled in the art would indeed understand that any position could be labeled using the isotopes cited by Noe:

(i) barbituric ring NH groups - H isotopes (^{2}H or ^{3}H) or N isotopes;

(ii) barbituric ring C=O oxygen atom – oxygen isotopes such as ^{17}O;

(iii) barbituric ring carbon atoms – carbon isotopes such as ^{13}C or ^{14}C;

(iv) R^{1} group - H, C, N, O, F and Cl isotopes;

(v) X group - H, C, N, O, F and Cl isotopes;

(vi) A group - H, C, N, O, F and Cl isotopes;

(vii) Y group - H, C, N, O, F and Cl isotopes;

(viii) B group - H, C, N, O, F and Cl isotopes;

(ix) G group - H, C, N, O, F and Cl isotopes.

Applicants contend that ascribing any teaching to Noe on selecting the 5-position for radiolabelling involves the invalid application of hindsight, based on the teaching of the present invention.

In addition, whilst Noe does mention the possibility of isotopic labeling, the person skilled in the art would know that these fall into various categories:

(i) non-radioactive isotopes;

deuterium (^{2}H), ^{13}C, ^{31}P, ^{17}O and ^{18}O.

(ii) radioactive isotopes

tritium (^{3}H), ^{14}C, ^{15}N, ^{32}P, ^{33}P, ^{18}F and ^{36}Cl.

Of these, only ^{18}F is an isotope suitable for *in vivo* radiopharmaceutical imaging as claimed in present claim 1. The vast majority of the teaching of Noe is thus outside the scope of the present claims. Applicants contend that the Examiner's identification of ^{18}F from Noe involves an invalid hindsight selection based on reading back from the subject matter of the present claims. There is no basis from within Noe itself to select ^{18}F over the many other isotopes , both radioactive and non-radioactive, taught by Noe.

As the Examiner has noted, Grams is silent on radiolabelled barbituric acid derivatives for PET imaging [emphasis added]. Hence, Grams is necessarily silent on which isotopes to attach and where.

Carpenter and Mobashery relate to MMPs which are structurally completely unrelated to barbituric acid derivatives. They too, can therefore provide no teaching on the site of radioisotope labeling to provide an *in vivo* imaging agent when the MMPi is a barbituric acid derivative. As argued above, Noe does not provide this teaching either. Consequently, no combination of Grams/Noe/Carpenter/Mobashery can provide the subject matter of present revised claim 1.

Finally, Applicants contend that any obviousness rejection which relies on the combination of 4 references is fundamentally flawed, since it demonstrates an invalid piecemeal approach wherein various features of the claims are identified in multiple prior art documents. Applicants contend that whilst motivation to combine could potentially exist for two documents, it is unrealistic for four.

Claim 29 stands rejected as being unpatentable over Grams [Biol. Chem., 382 p 1277-1285 (2001)] in view of Noe (US 6,706,723), in further view of Carpenter (US 6,656,448) and Mobashery (US 6,703,415) as applied above, in further view of Luthra et al. (US7,115,249) (Luthra).

Applicants respectfully submit the same argument as made previously. Grams is silent on radiolabelled barbituric acid derivatives for PET imaging [emphasis added]. Hence, Grams is necessarily silent on which isotopes to attach and where. Additionally, Noe is silent on imaging. Noe teaches instead the use of ^{3}H or ^{14}C labels for "drug and/or substrate tissue distribution assays". (Column 20 lines 39-41 therein). Noe teaches that ^{3}H or ^{14}C are particularly preferred labels (Column 20 lines 41-43). Thus, Noe teaches away from the subject matter of the present claims. Carpenter and Mobashery relate to MMPs which are structurally completely unrelated to barbituric acid derivatives. They too, can therefore provide no teaching on the site of radioisotope labeling to provide an *in vivo* imaging agent when the MMPi is a barbituric acid derivative. As argued above, Noe does not provide this teaching either. Consequently, no combination of Grams/Noe/Carpenter/Mobashery can provide the subject matter of present revised claim 1.

In view of the foregoing, it is respectfully submitted that 35 U.S.C. 103 rejections be withdrawn.

CONCLUSION

In view of the amendments and remarks herein, Applicants believe that each ground for rejection or objection made in the instant application has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections, and allowance of the current application are respectfully requested.

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,

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